

Criteria for Use Ticagrelor (Brilinta)

Criteria for Use
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

The Product Information should be consulted for detailed prescribing information. See the National VA PBM Monograph on this drug at www.pbm.va.gov or <https://vawww.cmopnational.va.gov/cmop/PBM/default.aspx/>

EXCLUSION CRITERIA (if ONE is checked, patient is not eligible)

- ☐ Active pathologic bleeding or history of bleed where risk of antiplatelet therapy outweighs the benefit
- ☐ History of intracranial hemorrhage (ICH)
- ☐ Moderate to severe hepatic impairment
- ☐ Concomitant simvastatin or lovastatin in doses >40 mg daily
- ☐ Concomitant use of strong CYP3A inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole)
- ☐ Concomitant use of strong CYP3A inducers (e.g., rifampin, dexamethasone, phenytoin, carbamazepine, and phenobarbital)
- ☐ Concomitant oral anticoagulation therapy
- ☐ Planned or prior fibrinolytic therapy (within the past 24 hrs)
- ☐ Increased risk of bradycardiac events (e.g., sick sinus syndrome, 2nd or 3rd degree AV block, bradycardic-related syncope not protected by a pacemaker)
- ☐ On dialysis
- ☐ Clinically important anemia or thrombocytopenia
- ☐ Hypersensitivity to agent
- ☐ Documented ongoing nonadherence to prior medications or medical treatment

INCLUSION CRITERIA (Restricted to Cardiology or local designee for initial VA prescription)

***Note*:** Clopidogrel is the preferred P2Y₁₂ inhibitor in the VA and should be selected unless there are compelling indications (to be adjudicated locally on a case by case basis) for using ticagrelor.

The following **MUST** be selected for patient to be eligible:

- ☐ Concomitant aspirin dose is 100 mg or less daily

AND patient meets criteria for one of the three indications below:

1. For ST-elevation myocardial infarction (STEMI) acute coronary syndrome (ACS), the following must be checked for patient to be eligible:
 - ☐ Patient with STEMI: persistent ST-segment elevation ≥1 mm (not known to be preexisting or due to a coexisting disorder) in ≥2 contiguous leads or new left bundle branch block (LBBB) and primary percutaneous coronary intervention (PCI) planned
2. For non-ST-elevation ACS (NSTEMI-ACS) or unstable angina (UA), 2 or more of the following must be selected for patient to be eligible:
 - ☐ ST-segment changes on electrocardiogram (ECG) indicating ischemia: ST-segment depression or transient elevation ≥ 1 mm in two or more contiguous leads
 - ☐ Positive biomarker indicating myocardial necrosis: Troponin I or T or CK-MB greater than the upper limit of normal and a history consistent with clinical MI
 - ☐ One of the following:
 - (a) ≥60 y of age
 - (b) Previous MI or coronary artery bypass graft (CABG) surgery
 - (c) Coronary artery disease with ≥50% stenosis in ≥2 vessels
 - (d) Previous ischemic stroke, transient ischemic attack (TIA) (hospital-based diagnosis), carotid stenosis (≥50%), or cerebral revascularization
 - (e) Diabetes mellitus
 - (f) Peripheral artery disease
 - (g) Chronic renal dysfunction
3. For stent thrombosis, the following must be checked for the patient to be eligible:
 - ☐ Definite or probable acute stent thrombosis (ARC definition)^a in patients documented to be compliant with aspirin and alternate P2Y₁₂ antagonist (ticagrelor plus aspirin is indicated)

For women of childbearing potential:

Determine pregnancy status prior to starting ticagrelor and provide contraceptive counseling. Discuss potential risk vs. benefit of ticagrelor treatment

during pregnancy. Women taking a ticagrelor should notify their provider if they become pregnant.

DOSAGE AND ADMINISTRATION

- 180 mg loading dose, then 90 mg orally twice daily
- 60 mg orally twice daily for patients with a **history of MI (one year or more after the event)** – See Issues for Consideration

MONITORING

- Patients should be monitored for signs and symptoms of bleeding, adherence, dyspnea, and bradycardiac adverse events (see Issues for Consideration).

ISSUES FOR CONSIDERATION

- Boxed warnings:**
 - Bleeding:** Ticagrelor may be associated with significant and sometimes fatal bleeding and should not be used in patients with a history of ICH. Bleeding events in the PLATO study with ticagrelor were similar or higher than clopidogrel. Consider other medications and conditions that increase bleeding risk. Ticagrelor should not be started in patients planned to undergo urgent CABG surgery and should be stopped 5 days before any surgery if possible.
 - Concomitant aspirin dose:** Aspirin doses above 100 mg daily are associated with reduced efficacy of ticagrelor. After the initial loading dose of aspirin, use with aspirin in doses of 75-100 mg daily.
- Interruption in therapy:** Unnecessary interruptions or discontinuations should be avoided. If ticagrelor must be discontinued (e.g., active pathological bleeding or surgery), restart therapy as soon as possible. Premature discontinuation of P2Y₁₂ inhibitors including ticagrelor in ACS patients confers an increased risk of cardiac events including stent thrombosis, MI, and death.
- Efficacy in U.S. population:** The U.S. population made up 8% of the pivotal PLATO study population. In contrast to the improved outcomes found with ticagrelor in non-U.S. patients, a trend of worse outcomes was observed in the U.S. subgroup. The primary endpoint of vascular death, MI, or stroke occurred in 11.9% of ticagrelor and 9.5% of clopidogrel patients (HR 1.27; 95% CI 0.92-1.75; p=0.146) in the U.S. subgroup. Additional post-hoc explorations of several baseline and clinical management variables found that only the higher aspirin dose used in the U.S. vs. non-U.S. patients among the variables explored in post-hoc analysis could account for the regional differences in outcomes. Overall, lower maintenance doses of aspirin were associated with lower event rates with ticagrelor, and higher maintenance doses of aspirin were associated with higher event rates with ticagrelor.
- Drug interactions:** CYP3A is the major enzyme responsible for the metabolism of ticagrelor and activation of its active metabolite. Both ticagrelor and its active metabolite are weak substrates and inhibitors of P-gp transporter. Avoid the concurrent use of CYP3A strong inhibitors (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir, telithromycin) and strong inducers (e.g., rifampin, dexamethasone, carbamazepine, phenytoin, phenobarbital). Avoid simvastatin and lovastatin in doses greater than 40 mg daily due to increased statin exposure and risk of adverse effects.
- Dyspnea:** Dyspnea was reported more frequently with ticagrelor than clopidogrel in PLATO (14% vs. 8%) and resulted in more treatment discontinuations, though overall rates of discontinuation were low (0.9% vs. 0.1%). If a patient develops dyspnea, other causes should be explored. If ticagrelor is suspected as the cause and the dyspnea is tolerable, no specific intervention is required. Treatment may be continued without interruption, but if dyspnea is intolerable, ticagrelor should be discontinued and another agent considered.
- Bradycardias:** Ticagrelor was associated with an increased risk of Holter monitor identified bradycardias in clinical trials, although clinical event rates were low. In the total PLATO study population where patients at risk of bradycardiac events were excluded, there was a nonsignificant excess of bradycardia and syncope adverse events reported with ticagrelor.
- Stroke or TIA:** Ticagrelor is not indicated for stroke or TIA. In a large, randomized controlled trial (SOCRATES), ticagrelor was not superior to aspirin in reducing the risk of recurrent vascular events (stroke, MI, or death) in patients with acute ischemic stroke or TIA. Similar rates of major, fatal, and intracranial bleeding were found in the ticagrelor and aspirin groups, though more patients on ticagrelor discontinued due to adverse events (mainly dyspnea or bleeding). Patients with a history of TIA/stroke are at higher risk of cardiovascular events and bleeding, including ICH. A significant excess of ICH with ticagrelor plus aspirin vs. clopidogrel plus aspirin was not found in the PLATO subgroup analysis of patients with TIA/stroke history, though the number of events was small. In the pivotal ACS trial (TRITON-TIMI 38), another novel antiplatelet agent, prasugrel (plus aspirin), was associated with a significantly increased risk of ICH vs. clopidogrel plus aspirin in patients with history of TIA/stroke and is contraindicated for use in these patients. In view of the evidence in ACS patients with a history of stroke or TIA, there is no compelling reason to select a newer antiplatelet agent over clopidogrel in patients with TIA/stroke history.
- Patients with a history of MI:** A lower dose of ticagrelor (60 mg twice daily) with aspirin is FDA approved for patients with a history of MI (at least one year ago) based on results from the PEGASUS TIMI-54 study. Enrolled patients had a previous MI and an additional high risk cardiovascular feature (e.g., age 65 or older, diabetes requiring medication, second prior spontaneous MI, multivessel coronary artery disease, chronic renal impairment) and were not at increased risk of bleeding. Patients who received dual antiplatelet therapy (DAPT) with ticagrelor plus aspirin had a lower risk of the composite outcome of cardiovascular death, MI, or stroke at 3 years (7.8% vs. 9.0%; HR 0.84; p=0.004; number needed to treat=79) compared to aspirin alone, at the expense of an increased risk of major (but not fatal) bleeding (2.3% vs. 1.1%; p<0.001; number needed to harm=81). DAPT patients were almost twice as likely to discontinue treatment due to adverse events (16% vs. 9%). Evaluating the increasing body of evidence available, extended DAPT therapy (beyond 1 year using ticagrelor, clopidogrel, or prasugrel) vs. aspirin alone is associated with a reduction in major adverse cardiovascular events in higher risk patients and an increase in major (but not fatal) bleeding. The optimal P2Y₁₂ antagonist for extended DAPT treatment is unclear, as there are no head-to-head studies available comparing P2Y₁₂ antagonists in patients who have suffered a remote (≥1 year) MI. In ACS populations, the risk of bleeding with clopidogrel is typically lower than with ticagrelor or prasugrel. Patients should be carefully selected for extended DAPT therapy balancing potential benefits and risks and should be re-evaluated regularly for changes in the benefit-to-risk ratio.
- Pregnancy Category C drug:** There are no studies of ticagrelor use in pregnant women. Animal studies revealed structural abnormalities of the fetus at maternal doses of 5 to 7 times the maximum recommended human dose. Ticagrelor should be used in pregnancy only if the potential

benefit justifies the potential risk.

- **Adherence to drug regimen:** Patients should be able to adhere to a twice daily drug regimen with ticagrelor. Adherence rates were high with ticagrelor in the pivotal PLATO trial, and it is unclear how outcomes may be affected with lower adherence rates, given the more rapid offset of action of ticagrelor.
- **Dual care patients:** All patients receiving the drug from VA should be managed according to the same standards (e.g., eligibility, monitoring, follow-up), consistent with the VHA National Dual Care Directive 2009-038.

RENEWAL CRITERIA

The American Heart Association (AHA)/American College of Cardiology (ACC) Guidelines for the management of NSTEMI-ACS and STEMI were published before PEGASUS and other more recent studies and meta-analyses examining different DAPT durations. The 2014 AHA/ACC Guidelines for NSTEMI-ACS recommend DAPT for up to 12 months for patients managed with an ischemia guided strategy and at least 12 months in patients who receive a stent during PCI. Longer durations may be considered in patients with stents.^b Conversely, shorter durations of DAPT may be reasonable in patients where the bleeding risk outweighs anticipated benefit. The 2013 AHA/ACC Guidelines for STEMI recommend DAPT for 12 months in patients who receive stents and up to 12 months in patients managed with fibrinolytic therapy.^c Ticagrelor was studied for a median duration of 277 days following ACS in the PLATO trial. See Issues for Consideration for additional information on patients with a history of MI in considering extended DAPT.

Select planned duration of therapy upon initiation of ticagrelor treatment:

- ☐ Planned duration of ≤12 months (**recommended**)
- ☐ Planned continuation beyond 12 months' duration (only after re-evaluation by Cardiology)

^a Academic Research Consortium (ARC): definite stent thrombosis-ACS with angiographic evidence of thrombus or occlusion; probable stent thrombosis-acute MI involving the target-vessel territory without angiographic confirmation

^b Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 ACC/AHA guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130:e344-e426.

^c O-Gara PT, Kushner G, Ascheim DD, et al. 2013 ACCF/AHA Guideline for the management of ST elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;61(4):e78-140